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DESCRIPTION

BENZOXEPINO-11-PIPERIDYLIDENE COMPOUNDS AND PROCESS FOR PRODUCTION THEREOF

Technical Field

The present invention relates to novel acid addition salts of 3-[4-(8-fluoro-5,11-dihydrobenz[b]oxepino[4,3-b]pyridin-11-ylidene)piperidino]propionic acid alkyl esters which are an intermediate for synthesizing 3-[4-(8-fluoro-5,11-dihydrobenz[b]oxepino[4,3-b]pyridin-11-ylidene)piperidino]propionic acid which is useful as an antiallergic agent of amphoteric type, as well as a process for production thereof and utilization thereof.

Background Art

It is known that 3-[4-(8-fluoro-5,11-dihydrobenz[b]oxepino[4,3-b]pyridin-11-ylidene)piperidino]propionic acid is useful as an antiallergic agent of amphoteric type (for example, see JP 6-192263 A and Journal of Medicinal Chemistry, Vol.38, No.3, pages 496-507). It is also known that, as an improved process for producing this compound, 8-fluoro-11-oxo-5,11-dihydrobenz[b]oxepino[4,3-b]pyridine is reacted

with 3-(4-oxo-piperidin-1-yl)-propionic acid ethyl ester in the presence of a low-valency titanium to give 3-[4-(8-fluoro-5,11-dihydrobenz[b]oxepino[4,3-b]pyridin-11-ylidene)piperidino]propionic acid ethyl ester and then the resulting compound is hydrolyzed, whereby the process steps are largely reduced, the reaction yield and the overall yield are largely improved, and the production efficiency is remarkably enhanced (see JP 2000-338574 A).

In the process described in JP 2000-338574 A which is an improved process, 8-fluoro-11-oxo-5,11-dihydrobenz[b]oxepino[4,3-b]pyridine is reacted with 3-(4-oxo-piperidin-1-yl)-propionic acid ethyl ester to give 3-[4-(8-fluoro-5,11-dihydrobenz[b]oxepino[4,3-b]pyridin-11-ylidene)piperidino]propionic acid ethyl ester, water and a base are added thereto, and the product is extracted with an organic solvent and then hydrolyzed to obtain an aimed compound. According to this process, however, a muddy insoluble matter is formed during the extraction. It was revealed that the insoluble matter is difficult to remove by filtration and, particularly in an industrial scale production, separation of the insoluble matter by filtration is very difficult. In addition, it was revealed

that a column purification step is necessary to remove the metals used in the process and the organic impurities which are mainly by-produced during production and thus the process is industrially disadvantageous.

For the above-mentioned reasons, it has been desired to develop an effective process for producing 3-[4-(8-fluoro-5,11-dihydrobenz[b]oxepino[4,3-b]pyridin-11-ylidene)piperidino]propionic acid or an acid addition salt thereof having such a purity that it can be used as a medicament on an industrial scale.

Disclosure of the Invention

An object of the present invention is to provide a process for producing 3-[4-(8-fluoro-5,11-dihydrobenz[b]oxepino[4,3-b]pyridin-11-ylidene)piperidino]propionic acid or an acid addition salt thereof having a high purity by effectively removing impurities and by-products which are produced or remain in the process, an intermediate for producing thereof, and a process for producing the intermediate.

The present inventors have recognized the importance of the process intermediate to minimize the time and loss

of compounds in the process for production of 3-[4-(8-fluoro-5,11-dihydrobenz[b]oxepino[4,3-b]pyridin-11-ylidene)piperidino]propionic acid or an acid addition salt thereof and to improve the production efficiency thereof and have intensively researched particularly on the purification step after the reaction. As a result, it has been found a process which goes through a novel acid addition salt of a 3-[4-(8-fluoro-5,11-dihydrobenz[b]oxepino[4,3-b]pyridin-11-ylidene)piperidino]propionic acid alkyl ester is excellent for separating the metals used in a synthetic reaction step and the by-products mainly accompanied by the production from the reaction liquid to complete the invention.

The present invention provides an acid addition salt of a 3-[4-(8-fluoro-5,11-dihydrobenz[b]oxepino[4,3-b]pyridin-11-ylidene)piperidino]propionic acid alkyl ester.

The present invention provides a process for producing an acid addition salt of a 3-[4-(8-fluoro-5,11-dihydrobenz[b]oxepino[4,3-b]pyridin-11-ylidene)piperidino]propionic acid alkyl ester which comprises reacting a 3-[4-(8-fluoro-5,11-dihydrobenz[b]oxepino[4,3-b]pyridin-11-

ylidene)piperidino]propionic acid alkyl ester with an acid.

Further, the present invention provides a process for producing 3-[4-(8-fluoro-5,11-dihydrobenz[b]oxepino[4,3-b]pyridin-11-ylidene)piperidino]propionic acid or an acid addition salt thereof which comprises hydrolyzing an acid addition salt of a 3-[4-(8-fluoro-5,11-dihydrobenz[b]oxepino[4,3-b]pyridin-11-ylidene)piperidino]propionic acid alkyl ester.

Best Mode for Carrying out the Invention

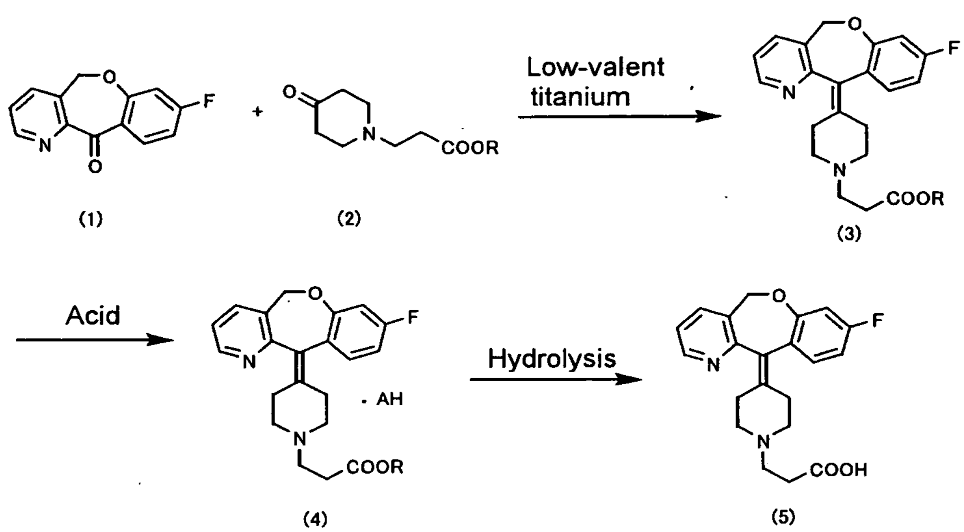
The alkyl group in the acid addition salt of a 3-[4-(8-fluoro-5,11-dihydrobenz[b]oxepino[4,3-b]pyridin-11-ylidene)piperidino]propionic acid alkyl ester (hereinafter, sometimes referred to as benzoxepino-11-piperidylidene compound), which is an ester residue of the benzoxepino-11-piperidylidene compound, is preferably a straight or branched C1 to C5 alkyl group, particularly ethyl group.

The acid addition salt of a 3-[4-(8-fluoro-5,11-dihydrobenz[b]oxepino[4,3-b]pyridin-11-ylidene)piperidino]propionic acid alkyl ester includes inorganic acid salts such as hydrochlorides, hydrobromides, phosphates and sulfates, and organic acid salts such as

methanesulfonates, p-toluenesulfonates and oxalates.

3-[4-(8-Fluoro-5,11-dihydrobenz[b]oxepino[4,3-b]pyridin-11-ylidene)piperidino]propionic acid ethyl ester hydrochloride is most preferable as the benzoxepino-11-piperidylidene compound.

The reaction scheme of the process for production of 3-[4-(8-fluoro-5,11-dihydrobenz[b]oxepino[4,3-b]pyridin-11-ylidene)piperidino]propionic acid or an acid addition salt which goes through a benzoxepino-11-piperidylidene compound, a novel intermediate of the present invention, is as follows:



wherein, R denotes an alkyl and AH denotes an acid.

Namely, 8-fluoro-11-oxo-5,11-dihydrobenz[b]oxepino[4,3-b]pyridin (1) is reacted with a

3-(4-oxo-piperidin-1-yl)-propionic acid alkyl ester (2) in the presence of a low-valent titanium to give a 3-[4-(8-fluoro-5,11-dihydrobenz[b]oxepino[4,3-b]pyridin-11-ylidene)piperidino]propionic acid alkyl ester (3), the resulting ester (3) is reacted with an acid to give the benzoxepino-11-piperidylidene compound (4) according to the present invention, and then the compound (4) is hydrolyzed to give 3-[4-(8-fluoro-5,11-dihydrobenz[b]oxepino[4,3-b]pyridin-11-ylidene)piperidino]propionic acid (5) or an acid addition salt thereof.

The reaction between compound (1) and compound (2) is effected by adding a mixed solution of compound (1) and compound (2) to a liquid mixture containing a low-valency titanium. The low-valent titanium used herein means a titanium having a valency of lower than 3 and may be generated in the reaction system by using a reducing agent and a halogenated trivalent or tetravalent titanium. Examples of the halogenated titanium include titanium chlorides such as titanium tetrachloride and titanium trichloride; and titanium bromides. Examples of the reducing agent include zinc, a zinc-copper alloy, magnesium, lithium and lithium aluminum hydride. As the

low-valent titanium, it is preferred, for example, to use those produced by reacting zinc or a zinc-copper alloy with titanium tetrachloride or titanium trichloride in the reaction system. The reaction between compound (1) and compound (2) is preferably carried out, in view of the yield of compound (3), by adding compound (1) and compound (2) to a heated mixture which is obtained by reacting a halogenated trivalent or tetravalent titanium with a reducing agent such as, for example, zinc or a zinc-copper alloy, preferably a heated mixture at a temperature in a range of from the temperature which is lower than the boiling point of the mixture by 10℃(boiling point minus 10℃) to the boiling point of the mixture.

Compound (3) is preferably used after the reaction liquid for synthesis is stirred with air bubbles in the presence of an organic base and then insoluble matters are separated from the reaction liquid. Examples of the organic base include amines, nitrogen-containing heterocyclic compounds and the like. The amines include mono(C1 to C6)alkylamines, di(C1 to C6)alkylamines, and tri(C1 to C6)alkylamines. The mono-, di- or tri-alkylamine is preferably triethylamine, tripropylamine,

diisopropylethylamine or the like and is particularly preferably triethylamine.

The time for stirring with air bubbles depends on reaction scale, but is preferably 0.5 to 5 hours, particularly 1 to 1.5 hours when air flow per kg of compound (1) is 25 to 200 L/min, particularly 30 to 70 L/min. Stirring with air bubbles prevents the reaction liquid from becoming viscous and makes the subsequent filtration procedure after addition of water smooth.

Separation of compound (3) from the reaction liquid is preferably effected by extraction with a water-organic solvent mixture. Examples of the organic solvent include low fatty acid esters such as ethyl acetate, propyl acetate, isopropyl acetate and butyl acetate. Ethyl acetate is preferred as the organic solvent.

The mixing ratio of water to the organic solvent, a ratio of water:organic solvent by volume, is preferably 1:2 to 2:1, and more preferably about 1:1.

Reaction of compound (3) with an acid gives the benzoxepino-11-piperidylidene compound of the present invention.

Examples of the acid include inorganic acids such as

hydrogen chloride, hydrogen bromide, phosphoric acid and sulfuric acid; and organic acids such as methanesulfonic acid, p-toluenesulfonic acid and oxalic acid. Preferred acids include hydrogen chloride, hydrogen bromide, methanesulfonic acid and p-toluenesulfonic acid.

The molar ratio of compound (3) to the acid is preferably in a range of from 1:1.5 to 1.5:1, more preferably in a range of from 1:1.1 to 1.1:1.

The reaction is preferably conducted with heating, more preferably with heating under reflux. Heating temperature is preferably from 30℃ to a reflux temperature of the solvent used, particularly from 70℃ to the reflux temperature. The time of the heating or heating under reflux varies depending on the reaction scale but is preferably 5 minutes to 1 hour, more preferably 5 to 20 minutes.

When compound (3) is mixed with the acid, the acid, particularly hydrogen chloride or hydrogen bromide, is preferably dissolved in an organic solvent. Examples of the organic solvent include lower alcohols such as ethanol, 1-propanol, 2-propanol and n-butanol; and lower fatty acid esters such as ethyl acetate, propyl acetate, isopropyl

acetate and butyl acetate. Ethanol, 2-propanol and ethyl acetate are preferred as the organic solvent.

The benzoxepino-11-piperidylidene compound (4) is particularly preferably prepared by mixing compound (3) dissolved in an organic solvent and the acid dissolved in an organic acid, heating the mixture under reflux, cooling the mixture, and filtering the mixture.

If purification of benzoxepino-11-piperidylidene compound (4) is insufficient, compound (4) is again incorporated with an organic solvent, heated preferably under reflux and then cooled to enhance purification efficiency. The organic solvent used may be any as long as it can dissolve benzoxepino-11-piperidylidene compound (4) during heating, and is preferably ethanol, 2-propanol or ethyl acetate.

By such simple procedure, it is possible to remove the metals used in the previous step and organic by-products from benzoxepino-11-piperidylidene compound (4). Since metals and organic by-products are sufficiently removed by simple operation without necessity of chromatography used in the production process described in JP 2000-338574 A, mass production is enabled and an actual production

efficiency in a factory is enhanced.

By hydrolyzing benzoxepino-11-piperidylidene compound (4), 3-[4-(8-Fluoro-5,11-dihydrobenz[b]oxepino[4,3-b]pyridin-11-ylidene)piperidino]propionic acid (hereinafter, sometimes referred to as merely piperidylidene propionic acid)(5) or an acid addition salt thereof is produced.

The hydrolysis is preferably conducted using an acid or a base. As the acid can be used hydrochloric acid, hydrobromic acid, sulfuric acid or phosphoric acid, and as the base can be used sodium hydroxide, potassium hydroxide or potassium carbonate.

The amount of the acid or the base used for the hydrolysis is preferably not less than 2 moles, more preferably 2 to 4 moles per mole of benzoxepino-11-piperidylidene compound (4).

Examples of the acid addition salt of piperidylidene propionic acid (5) include hydrochloride, hydrobromide, tartrate, methanesulfonate, and citrate.

Examples

Degree of purification of an organic compound was

measured by using high performance liquid chromatography (HPLC, product of Nippon Bunko) using acetonitrile, methanol or the like as a solvent and that of residual metals was measured by high-frequency plasma emission spectrometry (for example, OPTIM A-3300DV supplied by Parkin Elmer Inc., U.S.A.).

Example 1

3-[4-(8-Fluoro-5,11-dihydrobenz[b]oxepino[4,3-b]pyridin-11-ylidene)piperidino]propionic acid ethyl ester

To a suspension of zinc (17.8 g) in anhydrous tetrahydrofuran (180 mL) was added dropwise titanium tetrachloride (9.65 mL) under ice-cooling in an argon atmosphere. After the reaction mixture was stirred under reflux for 2 hours, to the boiling mixture was promptly added a solution of 8-fluoro-11-oxo-5,11-dihydrobenz[b]oxepino[4,3-b]pyridin (10.0 g) and 3-(4-oxo-piperidin-1-yl)-propionic acid ethyl ester (8.7 g) in anhydrous tetrahydrofuran (135 mL) under reflux. After heating under reflux for 30 minutes, the reaction mixture was cooled to room temperature, incorporated with triethylamine (56.5 mL) and ethyl acetate (350 mL), and stirred with bubbles of air stream at 1 L/min under

stirring at room temperature for 60 minutes. Precipitated insoluble matters were filtered through celite and washed twice with ethyl acetate (75 mL). The filtrate and the washing solution were combined and concentrated under reduced pressure, and to the residue was added ethyl acetate (350 mL) and water (350 mL), stirred at room temperature for 10 minutes. Precipitated insoluble matters were filtered through celite and washed twice with ethyl acetate (30 mL). An organic layer was separated from the combined mixture of the filtrate and the washing solution, an aqueous layer was extracted with ethyl acetate (100 mL), and the organic layer was combined therewith, washed with brine (75 mL), and then dried over anhydrous magnesium sulfate. After concentrating under reduced pressure, 8.65 g of the aimed product (85.8%, HPLC) was obtained as a brown viscous oil.

HPLC retention time: 5.9 minutes [column: Crestpack C18 T-5, 200mm; solvent: acetonitrile-0.1% aqueous phosphoric acid solution (containing 5 mmol/L of sodium 1-heptanesulfonate) (35:65), detection: UV (258 nm), flow rate; 1.0 mL/min]]

Example 2

3-[4-(8-Fluoro-5,11-dihydrobenz[b]oxepino[4,3-b]pyridin-11-ylidene)piperidino]propionic acid ethyl ester hydrochloride

To a solution of the brown viscous oil (8.65 g) obtained in Example 1 in ethanol (69 mL) was added dropwise at room temperature a 4 mol/L hydrogen chloride-ethyl acetate solution (5.1 mL, 1 equivalent reduced to quantitative purity). After the solution was stirred for 15 minutes at room temperature, it was heated and stirred under reflux for 10 minutes. After termination of heating, the solution was allowed to gradually cool to room temperature, and then ice-cooled and stirred for 30 minutes. The resulting crystals were filtered off, washed with cold ethanol (9 mL) and then dried at 50℃ under reduced pressure to give 6.9 g of the aimed product (98.0%, HPLC) as pale yellow crystals.

m.p.: 199-200℃

HPLC retention time: 5.9 minutes [column: Crestpack C18 T-5, 200 mm; solvent: acetonitrile-0.1% aqueous phosphoric acid solution (containing 5 mmol/L of sodium 1-heptanesulfonate)(35:65), detection: UV (258nm), flow rate; 1.0 mL/min].

Example 3

3-[4-(8-Fluoro-5,11-dihydrobenz[b]oxepino[4,3-b]pyridin-11-ylidene)piperidino]propionic acid hydrochloride

To an aqueous solution (16.6 mL) of sodium hydroxide (2.5 mol/L) was added the pale yellow crystals (6.4 g: 98.0%, HPLC) obtained in Example 2, and the resulting mixture was stirred for 1 hour at an internal temperature of 60℃. The reaction mixture was acidified with 6 mol/L of hydrochloric acid to pH 5 under ice-cooling, added with 51 mL of ethyl acetate and again added dropwise with 6 mol/L of hydrochloric acid to adjust the pH to 3.8. After precipitation of crystals, the solution was adjusted to a pH in a range of from 3.3 to 3.5 and stirred for 30 minutes. The resulting crystals were filtered and washed with 10 mL of isopropanol. The crystals thus obtained were dried under reduced pressure to give 5.82 g of the aimed product (99.6%, HPLC) as colorless crystals.

m.p.: 182-184℃

HPLC retention time: 6.1 minutes [column: Crestpack C18 T-5, 200 mm; solvent: acetonitrile-0.1% aqueous phosphoric acid solution (containing 5 mmol/L of sodium 1-

heptanesulfonate) (30:70), detection: UV (258nm), flow rate; 1.0 mL/min].

Example 4

3-[4-(8-Fluoro-5,11-dihydrobenz[b]oxepino[4,3-b]pyridin-11-ylidene)piperidino]propionic acid ethyl ester hydrochloride

The pale yellow crystals (0.2 g: 98.0%, HPLC) obtained in Example 2 was added to ethanol (1.6 mL) and the reaction mixture was heated under reflux for 30 minutes and then allowed to stand until it cooled to room temperature. The resulting crystals were filtered off and washed with ethanol (0.5 mL) to give 0.18 g of the aimed product (98.8%, HPLC) as colorless crystals.

m.p.: 199-201℃

HPLC retention time: 5.9 minutes [column: Crestpack C18 T-5, 200 mm; solvent: acetonitrile-0.1% aqueous phosphoric acid solution (containing 5 mmol/L of sodium 1-heptanesulfonate)(35:65), detection: UV (258nm), flow rate; 1.0 mL/min].

Example 5

3-[4-(8-Fluoro-5,11-dihydrobenz[b]oxepino[4,3-b]pyridin-11-

ylidene)piperidino]propionic acid ethyl ester p-toluenesulfonate

To a solution of 3-[4-(8-Fluoro-5,11-dihydrobenz[b]oxepino[4,3-b]pyridin-11-ylidene)piperidino]propionic acid ethyl ester (0.90 g: 89.9%, HPLC) obtained in Example 1 in ethyl acetate (7.2 mL) was added at room temperature p-toluenesulfonic acid (397 mg, 1 equivalent reduced to quantitative purity). The solution was stirred for 15 minutes at room temperature, and then heated and stirred under reflux for 10 minutes. After termination of heating, the reaction mixture was allowed to stand to gradually cool to room temperature, ice-cooled and stirred for 3 hours. The resulting crystals were filtered and washed with cold ethyl acetate (0.5 mL× 2). The resulting crystals were dried under reduced pressure at 50℃ to give 1.0 g of the aimed product (94.1%, HPLC) as reddish brown crystals.

m.p.: 87-89℃

HPLC retention time: 6.2 minutes [column: Crestpack C18 T-5, 200 mm; solvent: acetonitrile-0.1% aqueous phosphoric acid solution (containing 5 mmol/L of sodium 1-heptanesulfonate)(35:65), detection: UV (258nm), flow rate;

1.0 mL/min].

Example 6

3-[4-(8-Fluoro-5,11-dihydrobenz[b]oxepino[4,3-b]pyridin-11-ylidene)piperidino]propionic acid ethyl ester methanesulfonate

To a solution of 3-[4-(8-Fluoro-5,11-dihydrobenz[b]oxepino[4,3-b]pyridin-11-ylidene)piperidino]propionic acid ethyl ester (0.79 g: 89.9%, HPLC) obtained in Example 1 in ethyl acetate (6 mL) was added at room temperature methanesulfonic acid (176.2 mg, 1 equivalent reduced to quantitative purity). The solution was stirred for 15 minutes at room temperature, and then heated and stirred under reflux for 10 minutes. After termination of heating, the reaction liquid was allowed to stand to gradually cool to room temperature, ice-cooled and stirred for 2 hours. The resulting crystals were filtered and washed with cold ethyl acetate (0.5 mL× 2). The resulting crystals were dried under reduced pressure at 50℃ to give 0.83 g of the aimed product (94.0%, HPLC) as brown crystals.

m.p.: 156-166℃

HPLC retention time: 6.2 minutes [column: Crestpack C18 T-5, 200 mm; solvent: acetonitrile-0.1% aqueous phosphoric acid solution (containing 5 mmol/L of sodium 1-heptanesulfonate)(35:65), detection: UV (258nm), flow rate; 1.0 mL/min].

Example 7

3-[4-(8-Fluoro-5,11-dihydrobenz[b]oxepino[4,3-b]pyridin-11-ylidene)piperidino]propionic acid ethyl ester hydrobromide

To a solution of 3-[4-(8-Fluoro-5,11-dihydrobenz[b]oxepino[4,3-b]pyridin-11-ylidene)piperidino]propionic acid ethyl ester (0.81 g: 89.9%, HPLC) obtained in Example 1 in 2-propanol (6.5 mL) was added at room temperature an acetic acid solution (30%) saturated with hydrogen bromide (0.5 mL, 1 equivalent reduced to quantitative purity). The solution was stirred for 15 minutes at room temperature, and then heated and stirred under reflux for 10 minutes. After termination of heating, the reaction mixture was allowed to stand to gradually cool to room temperature, then ice-cooled and stirred for 1 hour. The resulting crystals were filtered off and washed with cold 2-propanol (0.4 mL×2). The

crystals thus obtained were dried under reduced pressure at 50℃ to give 0.60 g of the aimed product (97.9%, HPLC) as reddish brown crystals.

m.p.: 204-207℃

HPLC retention time: 6.2 minutes [column: Crestpack C18 T-5, 200 mm; solvent: acetonitrile-0.1% aqueous phosphoric acid solution (containing 5 mmol/L of sodium 1-heptanesulfonate)(35:65), detection: UV (258nm), flow rate; 1.0 mL/min].

Example 8

3-[4-(8-Fluoro-5,11-dihydrobenz[b]oxepino[4,3-b]pyridin-11-ylidene)piperidino]propionic acid ethyl ester

To a suspension of zinc (8.9 g) in anhydrous tetrahydrofuran (90 mL) was added dropwise titanium tetrachloride (4.8 mL) under ice-cooling in an argon atmosphere. After the reaction mixture was stirred under reflux for 2 hours, to the boiling mixture was promptly added a solution of 8-fluoro-11-oxo-5,11-dihydrobenz[b]oxepino[4,3-b]pyridin (5.0 g) and 3-(4-oxo-piperidin-1-yl)-propionic acid ethyl ester (4.35 g) in anhydrous tetrahydrofuran (68 mL) under reflux. After

heating under reflux for 30 minutes, the reaction mixture was cooled to room temperature, added with ice-water, and concentrated under reduced pressure to distill away THF. After addition of toluene (200 mL) and celite (10 g), the reaction liquid was made alkaline by adding K_2CO_3, and filtered through celite. Celite (15 g) was added to the filtrate, and then the filtrate was further filtered. An organic layer was separated from the filtrate, an aqueous layer was extracted with toluene (100 mL), and the organic layer was combined and washed with brine (40 mL), and dried over anhydrous $MgSO_4$. After distilling away the solvent under reduced pressure, 4.2 g of the aimed product (79.3%, HPLC) was obtained as a brown viscous oil.

HPLC retention time: 5.9 minutes [column: Crestpack C18 T-5, 200mm; solvent: MeCN-0.1% aqueous H_3PO_4 solution (containing 5 mM of sodium 1-heptanesulfonate)(35:65), detection: UV (258 nm), flow rate; 1.0 mL/min]]

Example 9

3-[4-(8-Fluoro-5,11-dihydrobenz[b]oxepino[4,3-b]pyridin-11-ylidene)piperidino]propionic acid ethyl ester hydrochloride

To a solution of the brown viscous oil (1.0 g)

obtained in Example 8 in ethanol (8 mL) was added dropwise at room temperature a 4M hydrogen chloride ethyl acetate solution (0.4 mL, 1 equivalent reduced to quantitative purity). The solution was stirred for 15 minutes at room temperature, and then heated and stirred under reflux for 10 minutes. After termination of heating, the reaction liquid was allowed to gradually cool to room temperature, then ice-cooled and stirred for 30 minutes. The resulting crystals were filtered off, washed with cold ethanol (1 mL), and dried under reduced pressure at 50℃ to give 0.54 g of the aimed product (92.8%, HPLC; quantitative purity[1)]: 92.6%) as pale yellow crystals.

Yield: 49.5%, substantial yield[2)]: 72.2%

Incidentally, 1) quantitative purity and 2) substantial yield have the following meanings:

1) Quantitative purity; Using a pure ethyl ester as a standard sample and confirming that the amount introduced to HPLC is proportional to the peak area of UV absorption, absolute quantitative determination is effected by using the ratio of the peak area of a test sample to that of the standard sample to give a quantitative purity.

(Calculation example: a pure standard sample of an ethyl

ester and a test sample having the same concentration are introduced in the same amount.

quantitative purity= (peak area of the test sample/peak area of the standard sample) ×100

Quantitative purity of a hydrochloride salt; a standard sample and a test sample having the same concentration are introduced in the same amount.

quantitative purity= (peak area of the test sample×a/peak area of the standard sample) ×100

a=molecular weight of the hydrochloride salt [432.92]/molecular weight [396.45]=1.092)

2) Substantial yield: a value which correctly reflects the amount of an aimed product obtained according to the present reaction by utilizing the quantitative purity.

substantial yield=quantitative purity after purification× yield/quantitative purity before purification

m.p.: 199-200℃

HPLC retention time: 5.9 minutes [column: Crestpack C18 T-5, 200 mm; solvent: MeCN-0.1% aqueous phosphoric acid solution (containing 5 mmol/L of sodium 1-heptanesulfonate) (35:65), detection: UV (258nm), flow rate; 1.0 mL/min].

Example 10

3-[4-(8-Fluoro-5,11-dihydrobenz[b]oxepino[4,3-b]pyridin-11-ylidene)piperidino]propionic acid ethyl ester hydrochloride

The pale yellow crystals (0.40 g; 92.8%, HPLC) obtained in Example 9 were added to ethanol (3.2 mL). After heating under reflux for 30 minutes, the reaction mixture was allowed to stand until it is cooled to room temperature. The resulting crystals were filtered and washed with ethanol (1 mL) to give 0.37 g of the aimed product (96.0%, HPLC; quantitative purity[1)]: 100%, remaining metals: Ti;<25ppm, Zn;<2.5ppm). Yield: 92.5%, substantial yield[2)]: quantitative

1), 2): quantitative purity and substantial yield are as mentioned above.

m.p.: 199-201℃

HPLC retention time: 5.9 minutes [column: Crestpack C18 T-5, 200 mm; solvent: MeCN-0.1% aqueous H_3PO_4 solution (containing 5 mmol/L of sodium 1-heptanesulfonate)(35:65), detection: UV (258nm), flow rate; 1.0 mL/min].

Reference example 1

Purification of 3-[4-(8-fluoro-5,11-

dihydrobenz[b]oxepino[4,3-b]pyridin-11-ylidene)piperidino]propionic acid ethyl ester

The brown viscous oil (1.0 g, 79.3%, HPLC) obtained in Example 8 was purified by column chromatography on NH silica gel (5.1 g) (chloroform: hexane=2:1) to give 928 mg of a pale brown oil (80.0%, HPLC; quantitative purity[1)]: 61.7%, remaining metals: Ti; 180ppm, Zn; 2.6ppm). Yield: 89.9%, substantial yield[2)]: 87.1%

1), 2): quantitative purity and substantial yield are as mentioned above.

HPLC retention time: 5.98 minutes [column: Crestpack C18 T-5, 200 mm; solvent: MeCN-0.1% aqueous H_3PO_4 solution (containing 5 mM of sodium 1-heptanesulfonate)(35:65), detection: UV (258nm), flow rate; 1.0 mL/min].

Industrial Applicability

By using as an intermediate an acid addition salt of a 3-[4-(8-fluoro-5,11-dihydrobenz[b]oxepino[4,3-b]pyridin-11-ylidene)piperidino]propionic acid alkyl ester to produce 3-[4-(8-fluoro-5,11-dihydrobenz[b]oxepino[4,3-b]pyridin-11-ylidene)piperidino]propionic acid, the metals used in the synthetic reaction step and the organic compounds mainly

by-produced during production are readily separated from a reaction mixture by a simple procedure, and the by-products are sufficiently removed without using a purification step by chromatography, whereby mass production is enabled and production efficiency is enhanced.